

REMARKS

Favorable reconsideration of this application is requested. Applicants appreciate the courtesy shown by Examiners Bertagna and Wilder in discussing this case with Applicants' representatives on June 25, 2008. The discussions of the interview are reflected in the following remarks.

Claims 1 and 9 have been amended. The limitation in claims 1 and 9 concerning $(X-Y)/X$ and $\{X-(Y-Y')\}/X$ being in a range of -1.00 to 1.00 is supported by for example page 14, line 16 to page 15, line 1 and page 19, line 27 to page 20, line 18 of the specification. The limitation in claims 1 and 9 concerning $(X+Y)$ being 30 or more is supported for example by page 14, lines 23-24 of the specification. The limitation in claims 1 and 9 concerning $(X+Y+Y')$ being 30 or more is supported for example by page 14, lines 33-35 of the specification. Claims 22 and 23 are new, and are supported for example by page 15, lines 6-7 of the specification.

As indicated during the interview, the "providing" steps in previous claims 1 and 9 have been deleted, and the relevant features thereof are included in the annealing steps. Claims 2, 3, 6, 10, 11, 12 and 15 have been amended accordingly.

Claims 18-21 are canceled. No new matter has been added. Claims 1-17 and 22-23 are pending.

Claim rejections - 35 U.S.C. § 103

Claims 1-7 and 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rabbani et al. (EP 0971039) in view of Notomi et al. (Nucleic Acids Research 2000; 28(12): e63). Applicants respectfully traverse the rejection.

Claim 1 requires a method using a primer that has, in the absence of an intervening sequence between the sequence (Ac') on the 3'-end portion of the primer and the sequence (B') on the 5'-side of the sequence (Ac') of the primer, a $(X-Y)/X$ value in the range of -1.00 to 1.00, and a $(X+Y)$ value of 30 or more where X denotes the number of bases in the sequence (Ac') and Y denotes the number of bases in the region flanked by the sequences (A) and (B) on the target nucleic acid sequence. Claim 1 further requires a method using a primer that has, in the presence of an intervening sequence between the sequence (Ac') and (B'), a $\{X-(Y-Y')\}/X$ value in the range of -1.00 to 1.00, and a $(X+Y+Y')$ value of 30 or more where X and Y have the same meaning as above, and Y' denotes the number of bases in the intervening sequence. Claim 9 similarly requires a method using a primer that has, in the absence of an intervening sequence

between the sequence (Ac') on the 3'-end portion of the first primer and the sequence (B') on the 5'-side of the sequence (Ac') of the first primer, a (X-Y)/X value in the range of -1.00 to 1.00, and a (X+Y) value of 30 or more, and in the presence of an intervening sequence between the sequences (Ac') and (B'), a {X-(Y-Y')}/X value in the range of -1.00 to 1.00 and a (X+Y+Y') value of 30 or more. Claim 9 further requires a method using a primer that has, in the absence of an intervening sequence between the sequence (Cc') on the 3'-end portion of the second primer and the sequence (D') on the 5'-side of the sequence (Cc') of the second primer, a (X-Y)/X value in the range of -1.00 to 1.00 and a (X+Y) value of 30 or more, and in the presence of an intervening sequence between the sequences (Cc') and (D'), a {X-(Y-Y')}/X value in the range of -1.00 to 1.00 and a (X+Y+Y') value of 30 or more, where X denotes the number of bases in the sequence (Cc'), Y denotes the number of bases in the region flanked by the sequence (C) and (D) on the target nucleic acid sequence, and Y' denotes the number of bases in the intervening sequence.

As indicated during the interview, the primer sequences required by claims 1 and 9 provide highly specific amplification in a short period of time. Our discussion is summarized as follows.

The experimental results of Examples 1, 2 and 3 of the present specification are compiled in the following table, which also includes the calculated X-Y/X and X+Y values for each of the primer numbers 1-40. Note that the results for Example 2, primers 23-26 and primer sets 12 and 13, only are presented for the sake of completeness and do not provide a comparison showing the advantages of the invention of claims 1 and 9.

Target	Primer No.	X	Y	X-Y/X	X+Y	Amplification time (min)	Primer set No.
SY153	1	20	-	-	-	Non specific	1
	2	20	-	-	-		
	3	20	0	1	20	60	2
	4	20	0	1	20		
	5	20	5	0.75	25	60	3
	6	20	5	0.75	25		
	7	20	10	0.5	30	40	4
	8	20	10	0.5	30		
	9	20	15	0.25	35	20	5
	10	20	15	0.25	35		
	11	20	20	0	40	40	6
	12	20	20	0	40		
	13	20	20	0	40	40	7
	14	20	20	0	40		
	15	20	20	0	40	40	8
	16	20	20	0	40		
	17	20	20	0	40	40	9
	18	20	20	0	40		
	19	20	20	0	40	40	10
	20	20	20	0	40		
	21	20	20	0	40	40	11
	22	20	20	0	40		
SY160	23	20	26	-0.3	46	90	12
	24	20	20	0	40		
	25	20	26	-0.3	46		
	26	20	20	0	40		
M13	27	24	50	-1.08	74	Non specific	14
	28	22	53	-1.41	75		
	29	24	0	1	24	90	15
	30	22	0	1	22		
	31	24	6	0.75	30	60	16
	32	22	6	0.73	28		
	33	24	12	0.55	36	60	17
	34	22	12	0.45	34		
	35	24	18	0.25	42	40	18
	36	22	18	0.18	40		
	37	24	22	0.08	46	60	19
	38	22	22	0	44		
	39	24	22	0.08	46	60	20
	40	22	22	0	44		

Referring to the above table as well as Figures 5 and 9 of the specification, primer sets 2 and 3, which do not satisfy X+Y of 30 or more, showed very little amplification of the targeted product of 160 base pairs after 60 minutes (see lanes 8 and 12 of Figure 5). In contrast, primer set 5, which satisfies X+Y of 30 or more, showed a significant amount of amplification product (as indicated by the strong signal at the targeted 160 base pair band) in as little as 20 minutes (see lane 19 of Figure 5). Moreover, primer set 14, which satisfies X+Y of 30 or more but not (X-Y)/X of -1 or more and 1 or less, showed a smear after 60 minutes of amplification, thereby indicating non-specific amplification. In addition, primer set 15, which does not satisfy X+Y of 30 or more, showed very little amplification of the targeted product of 240 base pairs after 90 minutes. In contrast, primer set 18, which satisfies X+Y of 30 or more, gave targeted amplification products in as little as 40 minutes, and a distinct signal at the targeted 240 base pair band after 60 minutes (see lane 20 of Figure 9).

Rabbani teaches isothermal amplification using the following primers:

FC (49 nt)

5'-CATAGCAGCA GGATGAAGAG GAATATGATA GGATGTGTCT GCGGCCTT-3'

RC (50 nt)

5'-TCCTCTAATT GCAGGATCAA CAACAACCAG AGGTTTGCA TGGTCCCGTA-3'.

The 19 and 20 bases at the 3' end of the FC and RC primers, respectively, are first segments that are capable of extension using HBV target DNA as a template. The 30 bases at the 5' ends of the FJ and RJ primers are second segments that are complementary to the first 30 bases synthesized by extension of the primers using HBV DNA as a template.

Applicants note that in paragraph [0118], Rabbani refers to the first segments on the 3' end of the FC and RC primers as being 29 and 30 bases, respectively, and the 30 bases on the 5' end of the FC and RC primers as being second segments that are complementary to the first 30 bases synthesized by extension of the primers. However, it is clear from the HBV genomic sequence (attached herewith) that the primer annealing sequence of the FC and RC primers is 19 and 20 base pairs in length, respectively. Also, in paragraph [0120], Rabbani refers to the 19 base sequence of LFC (LFC = 5'-GGATGTGTCT GCGGCCTT-3') and the 20 base sequence of the LRC (LRC = 5'- AGGTTTGCA TGGTCCCGTA-3') as corresponding to the first

segments of FC and RC primers, respectively. Thus, it can be clearly understood from this description as well as the HBV genomic sequence that in paragraph [0118], Rabbani erroneously refers to the first segments of the 3' ends of the FC and RC primers as being 29 and 30 bases, respectively, and in fact the lengths of the first segments should be 19 and 20 bases as indicated above.

As such, Rabbani's FC and RC primers give (X+Y) values of 19 (19+0=19) and 20 (20+0=20), respectively. On the other hand, claims 1 and 9 require the (X+Y) value to be 30 or more in the absence of an intervening sequence. Nothing in the reference teaches or suggests limiting the range of (X+Y) or (X+Y+Y') to be 30 or more as required by claims 1 and 9, nor any reason to limit the range of the {X-(Y-Y')}/X or the (X-Y)/X value and the (X+Y) or (X+Y+Y') value depending on the absence or presence of an intervening sequence within the primer so as to achieve efficient amplification. Accordingly, claims 1 and 9 and the dependent claims therefrom are patentable over Rabbani.

The rejection relies on Notomi for suggesting a modification to Rabbani that allegedly would bring Rabbani within the scope of the (X-Y)/X range of -1 to 0.5 in previous claims 1 and 9. This issue is moot in view of the revisions to claims 1 and 9, which restore the original range for (X-Y)/X and add the minimum requirement for X+Y. In any event, nothing in Notomi teaches or suggests limiting the range of the {X-(Y-Y')}/X or the (X-Y)/X value and the (X+Y) or (X+Y+Y') value depending on the absence or presence of an intervening sequence within the primer, nor any reason to expect that the superior amplification shown in the present specification can be achieved by limiting the primers as required by claims 1 and 9. Accordingly, claims 1 and 9 and the dependent claims therefrom are patentable over Rabbani and Notomi, taken alone or together.

Claims 8 and 17 are rejected under 35 USC 103(a) as being unpatentable over Rabbani et al. in view of Notomi et al. and further in view of Kool, E.T. (*Current Opinions in Chemical Biology* (2000) 4: 602-608). Applicants respectfully traverse the rejection.

Rabbani and Notomi have been distinguished above. Kool does not remedy the deficiencies of Rabbani and Notomi. Therefore, claims 8 and 17 are patentable over the references taken alone or together. Applicants do not concede the correctness of the rejection.

Favorable reconsideration and withdrawal of the rejection are respectfully requested.

In view of the foregoing, favorable reconsideration in the form of a notice of allowance is requested. Any questions or concerns regarding this communication can be directed to the attorney-of-record, Douglas P. Mueller, Reg. No. 30,300, at (612) 455.3804.

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PATENT TRADEMARK OFFICE

Respectfully submitted,

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Dated: July 21, 2008

Enclosure: HBV genomic sequence

LOCUS EU747320 3221 bp DNA circular VRL 09-JUN-2008
DEFINITION Hepatitis B virus isolate V51, complete genome.
ACCESSION EU747320

1 ttccactgcc ttcccccaag ctctgcagg tcccgagtc aggggttat atcttctgc
 61 ttgttgtcgg agttccggaa cagaatccc ttctgcgtt acatccatc acatctgc
 121 aatcccccgg aggactgggg accctgtac gaaatctgg aacatcacat caggatct
 181 aggaccctg ctcgttac aggggggtt ttctgttg acaagaatcc tcaataacc
 241 gtagatctt gactctgtt ggaattctt caatcttca gggggatcc cctgtgtt
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